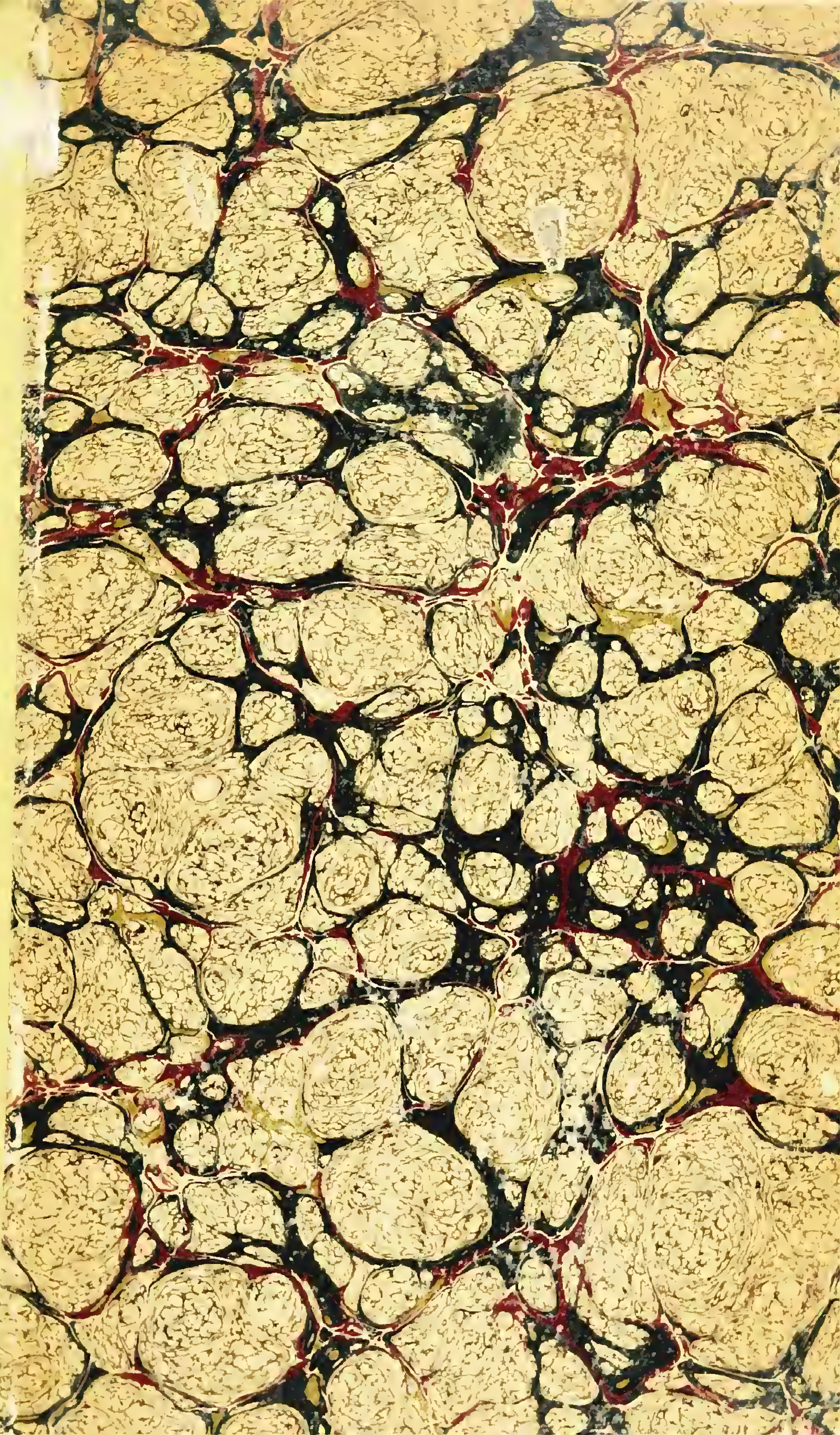

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Aus dem Laboratorium des Imperial Cancer Research Fund in London. Direktor: Dr. E. F. Bashford.

Einige Ergebnisse der experimentellen Krebsforschung.

Von

Dr. **E. F. Bashford**, Dr. **J. A. Murray** und Dr. **W. Cramer.**

(Sonderabdruck aus der Berliner klin. Wochenschr., 1905, No. 46.)

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Sonderabdruck aus der Berliner klin. Wochenschr., 1905, No. 46.

Aus dem Laboratorium des Imperial Cancer Research Fund in London. Direktor: Dr. E. F. Bashford.

Einige Ergebnisse der experimentellen Krebsforschung[1]).

Von

Dr. E. F. Bashford, Dr. J. A. Murray und Dr. W. Cramer.

Im Laufe der letzten 2½ Jahre haben wir mehr als 10 000 Uebertragungsversuche von bösartigen Geschwülsten gemacht. Das Material hierzu wurde uns von 12 spontanen und 4 transplantierten Mäusecarcinomen, sowie von 14 verschiedenen spontanen Carcinomen und Sarkomen von Ratten, Hunden, Katzen und Pferden geliefert. Es ist eine bemerkenswerte Tatsache, dass in unserer Erfahrung sich nur Mäusecarcinome als übertragbar erwiesen haben, obwohl wir mehr als 900 Versuche mit bösartigen Geschwülsten und Metastasen der anderen oben genannten Tierarten gemacht haben. In der Literatur finden sich zwar eine Reihe von Fällen, in welchen bösartige Geschwülste von Hunden und Ratten mit Erfolg transplantiert worden sein sollen. Im Lichte unserer heutigen Kenntnis halten dieselben jedoch einer eingehenden Kritik nicht Stand, da in allen diesen Fällen zwei wichtige Fehlerquellen nicht berücksichtigt worden sind.

Die für den Menschenkrebs eigentümliche Altersverteilung der Krankheitsgefahr besteht auch für den Krebs der Tiere. Dieser Tatsache ist aber von den meisten Forschern entweder keine Beachtung geschenkt worden oder sie haben absichtlich alte Tiere zu ihren Versuchen verwendet, in dem Glauben, dass dieselben einen günstigeren Boden für die transplantierten Krebszellen darbieten. Wir haben in unseren im vorigen Jahre veröffentlichten Arbeiten gezeigt, dass das Alter der Tiere ohne Einfluss auf den Erfolg der Transplantation ist und dass somit das Problem der Enstehung einer bösartigen Geschwulst von den Bedingungen, die ihr weiteres Bestehen bestimmen, scharf zu unterscheiden ist. Ehrlich und Apolant sind in einer kürzlich in dieser Wochenschrift veröffentlichten Arbeit zu dem gleichen Schluss gelangt. Die Verwendung alter Tiere bietet daher nicht den erhofften Vorteil; sie schliesst im Gegenteil die Gefahr in sich, dass eine spontane Geschwulst in den dem Experiment unterworfenen Tieren auftritt und eine erfolgreiche Transplantation vortäuscht. Besonders eklatant tritt der Irrtum, welcher durch die Nichtberücksichtigung der Altersverteilung des Krebses entstehen kann, in den zahlreichen Angaben über das endemische Vorkommen des Krebses bei Tieren zutage. Dies gilt sowohl für diejenigen Fälle, in welchen eine „Krebsepidemie“ spontan in einer Tierherde aufgetreten sein soll, als für die Versuche, durch Halten von Krebstieren mit normalen Tieren in einem Käfig eine solche Epidemie künstlich zu erzeugen. So hat Haaland, der absichtlich alte Tiere zu seinen Versuchen benutzt hat, bei solchen Versuchen positive Resultate erhalten, während in unseren Versuchen mit jungen Mäusen eine Uebertragung durch Zusamenleben in einem „Krebshaus“ nicht erzielt werden konnte. Auch die Versuche von Ehrlich und Apolant, die nur ganz junge Tiere verwendeten, sind negativ verlaufen.

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[1]) In Bezug auf Einzelheiten sei auf unsere früheren ausführlichen Publikationen: Proccedings of the Royal Society, 1904, Vol. 73, p. 66. Scientific Reports on the investigations of the Imperial Cancer Research Fund, London, Taylor and Francis, 1904 und 1905 verwiesen.

Die zweite Fehlerquelle liegt darin, dass es bei Tieren Neubildungen gibt, die unter dem Mikroskop von wahren bösartigen Geschwülsten kaum zu unterscheiden sind und deren wahre Natur erst durch die experimentelle Untersuchung zutage tritt. Wir haben eine solche Geschwulst, welche spontan an den Geschlechtsorganen von Hunden auftritt und durch den Coitus übertragen wird, einer eingehenden Untersuchung unterworfen. Dieselbe ist leicht übertragbar und sieht unter dem Mikroskop einem Rundzellensarkom täuschend ähnlich. Ein fundamentaler Gegensatz zwischen dieser Geschwulst und einer echten bösartigen Geschwulst tritt jedoch zutage, wenn man das Schicksal der eingeführten Zellen verfolgt.

Jensen war der erste, der diese Methode in seinen Untersuchungen über das von ihm transplantierte Mauscarcinom angewendet hat. Er hat gezeigt, dass bei dieser Geschwulst die eingeführten Zellen selbst wachsen und dass die Parenchymzellen der neuen Geschwulst völlig aus den Abkömmlingen der eingeführten Zellen gebildet werden. Wir haben diese Beobachtung für Jensen's Geschwulst und für verschiedene andere Mäusecarcinome bestätigt und darauf hingewiesen, dass hiermit ein experimenteller Beweis für die Anschauung, dass den Krebszellen im Gegensatz zu den Zellen der normalen Gewebe eine hrankenlose Wachstumsfähigkeit zukommt, erbracht worden r. Durch das Studium des infiltrierenden Wachstums und der etastasenbildung der transplantierten Mäusecarcinome sind wi der Anschauung gelangt, dass sich alle Eigenschaften des ebses aus dieser gesteigerten Wachtumsenergie ohne Zuhilfehme anderer Faktoren erklären lassen.

Verfolgt man dagegen das Schicksal der transplantierten llen der Hundegeschwulst, so zeigt sich, dass dieselben zum össten Teil, wenn nicht in ihrer Gesamtheit, degenerieren, ihrend — und das ist der springende Punkt — die die Transantationsstelle umgebenden Bindegewebszellen in Geschwulstllen umgewandelt werden. Der so aus den Zellen des neuen irtstieres gebildete Tumor wächst dann in den späteren Stadien r Geschwulstbildung aus sich selbst weiter. Die Uebertragung r Tumoren von einem Hund auf einen anderen ist daher nicht ie Transplantation, sondern eine Reaktion auf einen Infektionsrgang. Beiläufig sei noch bemerkt, dass sich diese Gewulst auch klinisch von einem echten Sarkom deutlich unterheidet. So ist die Krankheitsgeschichte unzweifelhaft die einer ektion; ferner tritt die Geschwulst spontan bei Hunden nur hrend der Zeit der Geschlechtsreife auf und zeigt eine Altersrteilung der Krankheitsgefahr, die von der den Sarkomen entümlichen Altersverteilung[1]) ganz verschieden ist. Die Gewult ist daher als eine bei Hunden vorkommende Geschlechtsnkheit anzusehen, die man vielleicht mit der Syphilis der nschen vergleichen darf.

Die experimentelle Methode gestattet somit eine einwandsie Unterscheidung zwischen echten bösartigen Geschwülsten l solchen infektiösen Granulomen, die ihnen histologisch ähn sehen. Die in der Literatur angegebenen Fälle von erfolgcher Uebertragung von Neubildungen an Hunden sind mit von uns untersuchten Geschwulst identisch. Von Uebertragungsversuchen an Ratten dürften allein Hanau's Experimente als gelungene Transplantationen einer echten bösartigen Geschwulst angesehen werden, wenn auch die oben erwähnten Fehlerquellen bei denselben nicht vermieden worden sind. Wir stehen daher vor der bedeutsamen Tatsache, dass die Uebertragung bösartiger Geschwülste bei der kurzlebigen Maus mit verhältnismässiger Leichtigkeit gelingt, bei Ratten nur sehr selten erfolgreich auszuführen ist, während sie bei Tieren mit längerer Lebensdauer bisher trotz zahlreicher Versuche immer erfolglos geblieben ist.

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[1]) Die statistischen Untersuchungen haben ergeben, dass die Sarkome gleiche Altersverteilung haben wie die Carcinome.

Die Mäusegeschwülste zeigen jedoch ebenfalls unter sich in bezug auf ihre Transplantationsfähigkeit und ihre Wachstumsgeschwindigkeit grosse Schwankungen, deren Extreme durch das sehr leicht übertragbare, schnell wachsende Mauscarcinom von Ehrlich und Apolant einerseits und durch die zahlreichen erfolglos übertragenen Mäusegeschwülste auf der anderen Seite dargestellt werden. Dazwischen stehen Geschwülste, wie Jensen's Carcinom, welche unschwer übertragbar sind, einen Durchschnittserfolg von ca. 30 pCt. geben und verhältnismässig schnell wachsen, während andere Carcinome, wie z. B. einige der von uns transplantierten Carcinome, nur sehr schwer transplantiert werden können, einen Durchschnittserfolg von 1/2 bis 2 pCt. haben und sehr langsam wachsen. Diese Schwankungen bestehen auch für bösartige Geschwülste desselben Organs, nämliche Carcinome der Mamma.

Die von uns mit Erfolg transplantierten Carcinome waren alle anaplastisch im Sinne von Hansemann's. Trotz dieser Entdifferenzierung besitzen jedoch die Zellen dieser Geschwülste noch Eigenschaften, welche die verschiedenen Geschwülste scharf charakterisieren. Während die transplantierten Parenchymzellen der Geschwulst, wie oben erörtert, in dem neuen Wirtstier weiter wachsen, degeneriert das mit ihnen eingeführte Bindegewebe1), und das Stroma der neuen Geschwulst wird von dem neuen Wirtstier gebildet. Das so gebildete Stroma ist für jeden einzelnen Tumor konstant und spezifisch, auch wenn die Transplantationen über mehrere Jahre hinaus ausgedehnt werden, und

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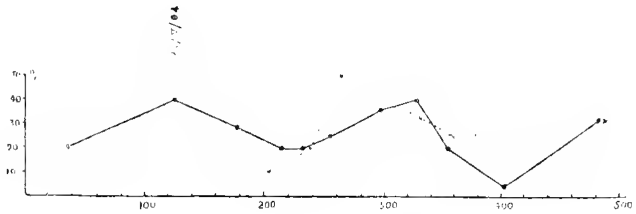
1) Der von Ehrlich und Apolant für die Entstehung eines Sarkoms auf dem Boden eines Carcinoms gegebene Erklärungsversuch, dass das mit den Krebszellen verpflanzte Bindegewebe durch die zahlreichen Tierpassagen eine bis zur Geschwulstbildung sich steigernde Proliferationskraft erfährt, steht daher mit den Tatsachen im Widerspruch.

lässt zwischen den verschiedenen Tumoren eine deutliche Unterscheidung zu, selbst dann, wenn die Parenchymzellen der Geschwülste histologisch nahe mit einander verwandt sind, z. B. bei Carcinomen desselben Organs. Die Spezifität der Stromareaktion zeigt zugleich, dass die Entdifferenzierung der Krebszellen nicht bis zur Undifferenzierung oder etwa bis zur Reversion in embryonales Gewebe gegangen ist.

Die Schwankungen in der Wachstumsenergie der verschiedenen Geschwülste desselben Organs wiederholen sich in ein und derselben Geschwulst zu verschiedenen Zeitpunkten. Unsere Beobachtungen an der Jensen'schen Geschwulst haben ein abwechselndes Steigen und Fallen der Wachstumsenergie aufgezeigt. Trägt man den Zeitraum in Tagen auf der Abreisse, den jeweiligen Erfolg von Transplantationen in Prozenten auf der Ordinate ab, so erhält man eine wellenförmige Kurve mit konstanter Wellenlänge (ca. 200 Tagen).



Die Wachstumsgeschwindigkeit ändert sich im gleichen Sinn wie die Erfolge bei der Transplantation.

Die Fähigkeit, Metastasen zu bilden, wechselt ebenfalls bei ein und derselben Geschwulst zu verschiedenen Zeitpunkten. Unser Material ist jedoch noch nicht gross genug, um eine einwandsfreie Beziehung zwischen den Schwankungen in der Wachtumsenergie der Geschwulst und der Metastasenbildung aufzustellen.

Von den mit Maustumoren arbeitenden Forschern haben bisher ausser uns nur Ehrlich und Apolant Aenderungen in der Wachstumsenergie beobachtet. Die von ihnen gefundene Zunahme haben sie im bakteriologischen Sinne als Virulenzsteigerung gedeutet. Da diese Autoren Einzelheiten über ihre Versuche noch nicht veröffentlicht haben, so ist es noch nicht möglich, festzustellen, ob dieser Zunahme eine Abnahme vorausgegangen resp. gefolgt ist.

Fassen wir die bei den Uebertragungsversuchen bösartiger Geschwülste erhaltenen Resultate über die Uebertragbarkeit derselben zusammen, wobei wir der Einfachheit halber nur Geschwülste eines Organs, der Mamma, berücksichtigen wollen, so finden wir

1. Schwankungen in der Uebertragbarkeit der Geschwülste bei Tieren verschiedener Arten,
2. Schwankungen in der Uebertragbarkeit der Geschwülste bei Tieren der gleichen Art,
3. Schwankungen in der Uebertragbarkeit ein und der gleichen Geschwulst.

Aus den negativen Uebertragungsversuchen bei Tieren mit längerer Lebensdauer darf nicht darauf geschlossen werden, dass diese Geschwülste überhaupt nicht übertragen werden können. Aus den Versuchen mit Mäusecarcinomen geht hervor, dass einerseits eine Transplantation gleichbedeutend mit einer künstlich ausgeführten Metastasenbildung ist, andererseits das Verschleppen von Krebszellen allein nicht genügt, um Metastasenbildung (oder eine erfolgreiche Transplantation) herbeizuführen, sondern dass hierzu ein gewisser Zustand der verschleppten Zellen notwendig ist. Da nun der Krebs von Hunden, Katzen etc. Metastasen bildet, so sind auch hier die Bedingungen für eine erfolgreiche experimentelle Uebertragung vorhanden. Nur sind diese Bedingungen, wie die zahlreichen negativen Versuche zeigen, bei den langlebigen Tieren seltener vorhanden wie bei der kurzlebigen Maus.

Abgesehen von der grösseren oder geringeren Seltenheit, mit welcher diese Bedingungen auftreten, ist auch die Anzahl der im übertragungsfähigen Zustand befindlichen Zellen für den Erfolg der Transplantation von Bedeutung. Hieraus dürfte sich wohl zum Teil das Verhalten der schwer transplantierbaren, langsam wachsenden Mäusecarcinome im Gegensatz zu den schnell wachsenden und leicht transplantierbaren Mäusegeschwülsten erklären. Wenn auch diese Ausführungen, dem negativen Charakter der Tatsachen, auf die sie sich stützen, entsprechend, nur mit Vorbehalt gegeben werden, so zeigen sie doch, dass auch die erfolglosen Uebertragungsversuche imstande sind, Aufschluss über das Krebsproblem zu geben. Falls unsere eben dargelegten Anschauungen richtig sind, so müsste auch die Krebsübertragung bei Hunden, Katzen etc. gelingen, wenn es möglich wäre, das

Tier während eines längeren Zeitraumes am Leben zu erhalten und gleichzeitig wöchentlich der Geschwulst Stücke zu entnehmen und auf eine genügend grosse Anzahl Tiere zu transplantieren.

Betrachten wir zum Schluss die Schwankungen in der Uebertragbarkeit und der Wachstumsenergie ein und derselben Geschwulst, so lassen sich hier mit grösserer Sicherheit Schlüsse ziehen. Es lässt sich durch Experimente beweisen, dass der Boden, auf welchen die Krebszellen verpflanzt werden, für den Erfolg der Transplantation ohne Bedeutung ist, solange nur Tiere der gleichen Rasse benutzt werden. Durch Ausschalten aller äusseren Faktoren werden mithin diese Schwankungen auf den Zellen innewohnende Eigenschaften zurückgeführt.

Man hat neuerdings, von chemischen Untersuchungen über die Fermentwirkung krebsiger Gewebe ausgehend, versucht, die Bösartigkeit einer Geschwulst, in welcher die meisten pathologischen Anatomen bisher nur einen Ausdruck der Wachstumsenergie gesehen haben, auf intracelluläre Eigenschaften chemischer Natur zurückzuführen. Im Sinne dieser Anschauung würde man daher die Schwankungen als Schwankungen in der Bösartigkeit der Geschwulst anzusehen haben. Das Experiment zeigt jedoch, dass die Bösartigkeit einer Geschwulst sich nicht unmittelbar auf intracelluläre Eigenschaften zurückführen lässt. Im Gegenteil: durch das Experiment lässt sich die Bösartigkeit vollständig von dem Wachstum einer Geschwulst trennen und durch Aenderung den experimentellen Bedingungen desselben wieder anfügen. So wächst z. B. Jensen's Carcinom selbst auf den Höhenpunkten der Wellenkurve, expansiv und metastasenbildend, aber nicht infiltrierend. Transplantiert man jedoch intraperitoneal oder lässt man die Metastasen sich weit genug entwickeln, so wachsen die so erhaltenen Geschwülste infiltrierend in die sie umgebenden Organe. Transplantiert man nun wieder eine solche infiltrierend wachsende Geschwulst subkutan, so wächst dieselbe wieder rein expansiv. Bei der experimentellen Untersuchung tritt also, soweit die intracellulären Eigenschaften der Krebszellen in Frage kommen, kein Unterschied zwischen dem rein expansiven („gutartigen") und dem infiltrierenden („bösartigen") Wachstum zutage. Die Bösartigkeit ist ein aus einer anthropocentrischen Ideenfolge entstandener Begriff, der weiter nichts ausdrückt als die Fähigkeit einer Geschwulst, den ihrem Wachstum durch ein Organ oder Gewebe entgegengestelltem Wider-stand mittels ihrer Wachstumsenergie zu überwinden. Fasst man den Begriff der Bösartigkeit in diesem Sinne auf, so sind Schwankungen in der Bösartigkeit und Schwankungen in der Wachstumsenergie synomym, nur dass man an Stelle der messbaren Wachstumsenergie einen unmessbaren Begriff setzt.

Die intracellulären Vorgänge aufzuklären, die diesen Schwankungen zugrunde liegen, muss ferneren Arbeiten vorbehalten werden. In dem periodischen Steigen und Fallen der Wachstumsenergie sehen wir jedoch einen deutlichen Hinweis darauf, dass das schrankenlose Wachstum der Krebszellen nicht ein kontinuierlicher, vegetativer in der Tierwelt ohne Analogie dastehender Vorgang ist, sondern dass es aus einer Reihe cyklischer Vorgänge besteht, in welchen sich an einer Zellart das Phänomen wiederholt, welches uns im Metazoenorganismus als Kontinuität der Arten entgegentritt.

Druck von L. Schumacher in Berlin N. 24.

Aus dem Laboratorium des Imperial Cancer Research Fund in London. Direktor: Dr. E. F. Bashford.

Einige Bemerkungen zur Methodik der experimentellen Krebsforschung.

Von

E. F. Bashford.

(Sonderabdruck aus der Berliner klin. Wochenschr., 1906, No. 16.)

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Aus dem Laboratorium des Imperial Cancer Research Fund in London. Direktor: Dr. E. F. Bashford.

Einige Bemerkungen zur Methodik der experimentellen Krebsforschung.

Von

E. F. Bashford.

In der Berliner klin. Wochenschr., 1905, No. 28, kündigten Ehrlich und Apolant die Entstehung eines Sarkoms während fortgesetzter Carcinomimpfungen bei Mäusen an. Sie haben diese Erscheinung in folgender Weise zu erklären versucht.

1. „Wenn wir nach einer Erklärung des Vorganges suchen, so kann natürlich der direkte Uebergang der Krebs- in die Sarkomzelle ernsthaft nicht diskutiert werden. Fraglich bleibt es jedoch, ob sich nicht im Laufe der stetig fortgesetzten Impfungen der Chemismus der Carcinomzellen so ändert, dass Stoffe gebildet werden, die reizend auf die Bindegewebszellen einwirken und dieselben zu metaplastischer Wucherung veranlassen.“

2. „Eine weitere Erklärungsmöglichkeit besteht darin, dass bei den fortgesetzten Transplantationen neben den Krebszellen auch Bindegewebe verpflanzt wird, das durch die zahlreichen Tierpassagen im fremden Organismus eine bis zur Geschwulstbildung sich steigernde Proliferationskraft erfährt.“

Zu diesem zweiten Erklärungsversuch habe ich in No. 46, 1905, folgendes bemerkt:

„Während die transplantierten Parenchymzellen der Geschwulst, wie oben erörtert, in dem neuen Wirtstier weiterwachsen, degeneriert das mit ihnen eingeführte Bindegewebe[1]), und das Stroma der neuen Geschwulst wird von dem neuen Wirtstier gebildet“.

In No. 2, 1906, dieser Wochenschrift kommt Ehrlich auf die Sarkomentstehung wieder zurück und greift mich in einer Fussnote wegen der von mir geübten Kritik an.

Indem ich den gereizten Ton der diesbezüglichen Bemerkungen Ehrlich's bedauere, will ich im Interesse einer sachlichen Diskussion darauf verzichten, die in dieser Fussnote gemachten zahlreichen Irrtümer richtig zu stellen. Dass Ehrlich den von uns kritisierten Erklärungsversuch fallen gelassen hat, ist für mich Rechtfertigung genug.

Die von uns gemachten Bemerkungen stützen sich auf eine Methode, welche darin besteht, dass während der ersten Wochen nach der Transplantation einer Geschwulst die Impfstelle während einer Reihe verschiedener Zeitpunkte systematisch untersucht wird. — Es wird, um ein konkretes Beispiel zu geben, eine Geschwulst auf 390 Mäuse transplantiert und je 5 Tiere werden 2 Stunden, 4, 8, 16, 24 Stunden, 1 Tag, 2, 3 Tage usw. nach der Transplantation getötet. Die transplantierten Zellen, die mit einiger Uebung leicht gefunden werden können, werden fixiert und mikroskopisch an lückenlosen Schnittserien untersucht. Auf diese Weise erhält man ein Material, welches eine einwandfreie Beurteilung der verschiedenen Faktoren, welche bei der Bildung der neuen Geschwulst mitwirken, gestattet. Dieser Methode, welche zuerst von Jensen angewendet worden ist, wird seit Anfang 1903 in meinem Institut nicht nur jeder transplantierte Tumor unterworfen, sondern auch ein und derselbe Tumor wird in verschiedenen Generationen derart untersucht. Einige der so erhaltenen Resultate habe ich gemeinsam mit Murray und Cramer in unseren ausführlichen Mitteilungen mitgeteilt und durch eine Reihe von Abbildungen erläutert, so dass eine objektive Prüfung der von mir gemachten Angaben möglich ist. Von anderen Forschern auf diesem Gebiet, Jensen ausgenommen, sind derartige systematische Untersuchungen nicht gemacht, jedenfalls nicht veröffentlicht worden.

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[1]) „Der von Ehrlich und Apolant für die Entstehung eines Sarkoms auf dem Boden eines Carcinoms gegebene Erklärungsversuch, dass das mit den Krebszellen verpflanzte Bindegewebe durch die zahlreichen Tierpassagen eine bis zur Geschwulstbildung sich steigernde Proliferationskraft erfährt, steht daher mit den Tatsachen im Widerspruch.“

Dies ist um so bemerkenswerter, als diese Methode die Entscheidung über eine Reihe strittiger Probleme gestattet, oft sogar das einzige Mittel ist, um festzustellen, ob man es mit einer bösartigen Geschwulst oder mit einem infektiösen Granulom zu tun hat. Ferner ist es müssig, über die Wachstumsenergie der Geschwulstzellen in gewissen Fällen zu diskutieren, bis die Möglichkeit ausgeschlossen ist, dass nicht bei jeder Ueberimpfung neue Zellen den geschwulstartigen Wachstumsmodus übernehmen.

Wir haben auf diese Weise gezeigt, dass das mit den Parenchymzellen eines Mäusecarcinoms eingeführte Bindegewebe degeneriert und haben bis jetzt keine Ausnahme von dieser Regel gefunden. Ehrlich und seine Mitarbeiter behaupten, dass gelegentlich eine solche Abweichung von der Regel vorkommt und in den von ihnen angegebenen Fällen eine Sarkomentstehung auf dem Boden eines Carcinoms vorliegt. Ein Beweis für diese Behauptung wird jedoch von ihnen nicht beigebracht.

Wir haben ferner die von Jensen gefundene Tatsache bestätigt, dass die Parenchymzellen eines transplantierbaren Carcinoms nicht degenerieren, sondern dass sie aus sich selbst weiterwachsen, so dass sich die Parenchymzellen der neuen Geschwulst allein aus den eingeführten Zellen ableiten. Diese Methode gestattet daher eine deutliche Unterscheidung zwischen den Parenchymzellen und den Stromazellen einer bösartigen Geschwulst und lässt, falls man dieselbe zu verschiedenen Zeitpunkten während der Züchtung des Tumors anwendet, eine etwa aufgetretene Veränderung in den Parenchymzellen bzw. Stromazellen deutlich erkennen. Beobachtet man jedoch eine solche Aenderung nur bei gelegentlich vorgenommener histologischer Prüfung, so ist man für eine Erklärung etwaiger schon aufgetretener Veränderungen im Parenchyma oder Stroma auf Hypothesen angewiesen.

Ich habe in Vorstehendem einige der Fehlerquellen angegeben, die der experimentellen Krebsforschung anhaften, und gezeigt, wie dieselben eliminiert werden können. Von Ehrlich und seinen Mitarbeitern ist keine dieser Fehlerquellen vermieden worden. Da im Gegensatz zu den von Jensen, Borrel, Michaelis und anderen Forschern gezüchteten Tumoren für die aus Mäusecarcinomen entwickelten Sarkome das Material allein in den Händen der Frankfurter Forscher ist, so können wir nur von diesen eine Lösung der oben berührten Fragen erwarten. Bis dahin ist eine Entscheidung darüber, ob die von ihnen beobachteten Geschwülste 1. von Anfang an Mischgeschwülste waren oder ob 2. ein infektiöses Granulom sich auf dem Boden eines Carcinoms gebildet hat oder ob 3. ein wahres Sarkom aus eingeführtem Stroma oder Reaktionsgewebe des Wirtes während der Uebertragung eines Carcinoms entstanden, nicht möglich.

Dass ein Sarkom während der Uebertragung eines Carcinoms entstehen kann, ist a priori nicht unmöglich und deckt sich ganz mit der von mir vertretenen Anschauung, dass das Altern der Gewebe eine notwendige Vorbedingung für die Bildung bösartiger Geschwülste ist. Das schnelle Wachstum des ursprünglichen Mäusecarcinoms hat die Proliferationsfähigkeit des Bindegewebes einer Maus erschöpft; das Bindegewebe ist in den Zustand der Senilität versetzt worden, aus dem es durch sarkomatöse Entartung befreit wird.

Schon im März 1904 und April 1905 habe ich eine Steigerung der Transplantationsfähigkeit nach fortgesetzten Tierpassagen beschrieben; doch kann ich Ehrlich's bakteriologischer Deutung dieses Phänomen als Virulenzsteigerung vorläufig nicht zustimmen.

Bereits vor $1^1/_2$ Jahren sind in meinem Institut Geschwulsttransplantationen in Zwischenräumen von 6—12 Tagen gemacht worden. Die damalige grosse Wachstumsenergie der Geschwulst war jedoch nicht eine Folge der beschleunigten Tierpassagen, sondern der Ausdruck eines den Geschwulstzellen innewohnenden scheinbar periodisch wiederkehrenden Zustandes, der von uns bereits beschrieben worden ist. Unter gewissen Kautelen lassen sich Geschwülste auch in fremden Tierrassen züchten; dass aber dadurch Abschwächung der Virulenz im bakteriologischen Sinne zu erreichen ist, ist in unseren Experimenten nicht vorgekommen[1]), indem nach zahlreichen Tierpassagen die ursprüngliche, höhere Wachstumsenergie für die Stammrasse beibehalten bleibt.

Natürlich müssen für die Verwertung der Resultate solcher Versuche im Sinne einer Steigerung oder Abschwächung des Tumorenwachstums die Schwankungen, die auf innewohnenden Zelleigenschaften beruhen, durch geeignete Kontrollversuche ausgeschaltet werden.

Es wäre jedoch müssig, solche Fragen zu diskutieren, ehe die Gewähr da ist, dass hier tatsächlich ein Sarkom entstanden ist.

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1) Anmerkung bei der Korrektur: Inzwischen hat Ehrlich übereinstimmende Ergebnisse in seinem Vortrag im Kaiserin-Friedrichhaus mitgeteilt.

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[*From the* PROCEEDINGS OF THE ROYAL SOCIETY, B, VOL. 77, 1906.]

On the Occurrence of Heterotypical Mitoses in Cancer.

BY E. F. BASHFORD, M.D., AND J. A. MURRAY, M.B., B.SC.

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On the Occurrence of Heterotypical Mitoses in Cancer.

By E. F. BASHFORD, M.D., and J. A. MURRAY, M.B., B.Sc.

(Communicated by J. Rose Bradford, M.D., F.R.S. Received November 2,—Read November 23, 1905.)

[PLATES 5 AND 6.]

The present paper refers to a communication* made to the Royal Society in January, 1904. In that paper and its expansion,† published later, we emphasised the significance of the zoological distribution of cancer; we discussed the unique features of the processes responsible for the experimental transmission of carcinoma from one animal to another and the limitations to its successful attainment: we also published a series of figures depicting the characters of the nuclei of cancer cells during division, in the malignant new growths of fishes and mammals. We shall give a different explanation of the mitoses we figured in our earlier communications as resembling the heterotypical mitoses of reproductive tissue. We have found that those mitoses may be interpreted as somatic mitoses with longitudinally split chromosomes. Their apparent heterotypical form is thus due to variations in the development of the achromatic figure, the peculiar form of the chromosomes and their mode of attachment to the spindle.

Our figures of heterotypical mitoses in cancer confirmed the observations of Farmer, Moore and Walker, communicated‡ to the Royal Society at the preceding meeting, but we dissociated ourselves from their conclusions on the diagnostic value and the significance of the phenomenon. The amount of chromatin entering into the equatorial plate of the dividing cells of human cancer had long been known to be subject to diminution (von Hansemann,§ 1893), but the presence of heterotypical mitoses appeared to throw a new light on its occurrence and meaning.

We have pointed out that the characteristic changes accompanying the heterotypical mitosis in the reproductive tissues are absent from cancer cells undergoing what we regarded as this form of division, and that the want of correspondence extends to the stages which precede and follow it.|| We have

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* 'Roy. Soc. Proc.,' vol. 73.

† First Scientific Report, Cancer Research Fund.

‡ 'Roy. Soc. Proc.,' vol. 72.

§ 'Studien über die Spezificität, den Altruismus und die Anaplasie der Zellen,' Berlin, 1893, etc.

|| *Loc. cit.*, and 'Lancet,' April 1, 1905.

also illustrated some of the appearances simulating bivalent chromosomes, but in reality conforming to the type met with in ordinary (somatic) karyokinetic cell-division.* In what follows we shall illustrate other sources of error on the basis of a renewed analysis of the preparations from which the figures of heterotypical mitosis in our previous papers were made and by other figures not yet published.

In the sexual cells of animals the heterotypical mitosis is preceded by a stage known as the "synapsis." In it the chromatin filament is split longitudinally and gathered into a rosette at one part of the nucleus, the nucleolus lying to one side and usually flattened against the nuclear membrane. In this stage the chromosomes are believed to unite in pairs, thus giving rise in the equatorial plate of the heterotypical mitosis to bivalent chromosomes, half as numerous as those characteristic of ordinary somatic cells. The examination of many sporadic and transplanted malignant new growths failed to reveal a corresponding sequence in their nuclei. We therefore undertook a renewed analysis of the preparations of the stages in cell-division already figured from transplanted mouse tumours, and of other preparations resembling them, to determine whether or not their identification as heterotypical were justified. We shall confine our statements mainly to five transplantable mouse tumours because they permit of control observations with varying methods of preservation and staining in a manner not possible with material from sporadic new growths; but our remarks apply also to the figures we have published from sporadic tumours of the trout and cat.

Von Hansemann† has combated the statements on the presence of heterotypical mitoses in malignant growths, and ascribes the appearances figured to clumping of the chromosomes, and to pathological abnormalities in their form. He adheres to his conclusion that the numerical diminution is not an exact halving of the normal number, but is irregular, and due to (1) asymmetrical mitosis, and (2) casting out and degeneration of chromosomes. Häcker reproduced three of our figures in a paper in which he admitted the striking similarity to heterotypical mitosis, but suggested that adhesion of the chromosomes in pairs,‡ together with longitudinal splitting of the couples thus produced, might account for the phenomena encountered in cancer. The appearances in some preparations are explicable in the manner suggested by von Hansemann,* but all the forms of cell-division resembling the heterotypical mitoses of reproductive tissue cannot be accounted for in this manner.

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* *Loc. cit.*

† 'Biolog. Centralb.,' vol. 24, 1904; vol. 25, 1905; 'Verhandl. physiol. Ges.,' Berlin, 1904.

‡ Häcker uses the term "heterotypical" in a purely morphological sense, and embraces in it the mitoses of the cells destined to give rise to the sexual products of Ascaris and the Copepods. In the latter he has shown that exposure to ether ('Anat. Anzeiger,' 1900) may cause all the cells of the developing egg to exhibit this modification (viz., cohesion of the chromosomes in pairs). In the strict sense of the word, the term "heterotype" is

Some of the nuclear divisions previously figured have been found on re-examination to be due to an artificial grouping together of distinct chromosomes. Fig. 1, reproducing at higher magnification fig. 3 of our Royal Society paper, and fig. 27 of the First Scientific Report of the Imperial Cancer Research Fund, affords an example of this source of confusion. The chromosomes seem to be bivalent, *i.e.*, to have the form of rings and loops. This mitosis is not completely depicted in fig. 1, the remainder of the chromosomes being in the next section. The preparation has been carefully restained. The result is shown in figs. 2 and 3. The "rings" and "loops" resolve themselves into a larger number of ordinary short chromosomes, split longitudinally. The dense equatorial plate of the next section shows clearly the presence of many short chromosomes split longitudinally, and arranged in the manner described below. The mitosis is therefore somatic, and not heterotypical.

The ordinary scheme of karyokinetic cell-division presents, in its phase of equilibrium (amphiaster or equatorial plate), a series of V-shaped loops with limbs of equal length, arranged around a central spindle and all lying in a plane at right angles to its axis. This arrangement is by no means universal. Some of the deviations are of great importance to a proper understanding of what occurs in cancer. Frequently the limbs of the V-shaped loops are of unequal length. When this is the case the attraction fibres are relatively few in number and attached only to the apex of the V and its immediate vicinity, and therefore nearer one end of each chromosome than the other.

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applied to the form of mitosis characteristic of the first ripening division of the spermatocytes of amphibia, as first described by Fleming. In the Salamander, ring-shaped chromosomes, half as numerous as the longitudinally split chromosomes of somatic mitoses, are stretched out into elongated ellipses upon the spindle, giving rise to a barrel-shaped figure. Chromosomes of similar form are associated with their numerical reduction in many animals and plants, but it must be borne in mind that different forms of chromosomes occur in the corresponding mitoses of some animals. In *Ascaris*, *e.g.*, both ripening divisions appear to be effected by a longitudinal splitting of chromosomes arranged transversely on the spindle, and in others ring or loop chromosomes are never formed. It was, of course, conceivable that reduction-divisions might occur in cancer by means of chromosomes unlike those in the reproductive tissues of the same animal. The frequency of cells with diminished numbers of chromosomes led us to examine many tumours for evidence of their occurrence, but without result.

* 'Biolog. Centralb.,' vol. 24, 1904.

As a consequence the longer limb does not come to a position of equilibrium in the equatorial plane, but may take up one inclined to the axis of the achromatic figure. When the attraction fibres are attached to the chromosomes in this manner in a cell of elongated form, the longer limbs may even come to lie parallel to the spindle axis, and nuclear divisions closely resembling heterotypical mitoses may result. In such mitoses pairs of distinct chromosomes whose longer limbs lie on opposite sides of the equator, while their apices are closely opposed, simulate bivalent chromosomes, *cf.* figs. 5 to 10. In polar view the apparent halving of the chromosome number due to superposition, and the unusual vertical extension of the free longer limbs, are even more deceptive; unless the longitudinal splitting of the chromosomes is very clear, the resemblance to heterotypical mitoses may be almost perfect. During the separation of the daughter chromosomes such nuclear divisions are especially deceptive, because the longer limbs adhere for some time after separation of the apices and short limbs. Barrel-shaped forms result, in which the crowding together of the chromosomes renders their enumeration impossible, but at the same time conveys the impression of a diminution in their number.

A much more serious source of error results from individual differences in the size of the chromosomes in one and the same nucleus. Montgomery* and Sutton† have drawn attention to this phenomenon in the sexual cells of invertebrates. We have found it to be present also in many vertebrate mitoses. When the chromosomes attain the position of equilibrium in the equatorial plate the smaller take up a position nearer the axis of the central spindle than the larger or more massive ones. Seen in profile the larger may then completely screen the smaller from view, and lead to an underestimate of the chromosome number.

Normally, nuclear division takes place by means of bipolar mitosis distributing the halves of the chromosomes to two daughter nuclei. An interesting abnormality results, when, from any cause, this segregation of the daughter elements does not take place. This may either result from the centrosome, remaining single or, if after division of the centrosome, one only become attached to the chromosomes by the attraction fibres. The chromosomes then remain in one group, but the daughter elements separate slightly from each other before combining to form one large nucleus, containing twice as many chromosomes as the mother nucleus. This form of mitosis, known as a "monaster" (from the presence of only one active attraction sphere) has been studied and described in detail by Th.* and M.† Boveri in invertebrates: figs. 13, 14, and 15, from a squamous cell carcinoma of the tongue (human), represent a cell in this condition. The nuclear membrane has disappeared, but there is no trace of radiations or centrosomes to be seen. The chromosomes are arranged as a hollow sphere around a central clear area, and for the most part consist of two parallel daughter elements in different stages of separation. Some chromosomes in which the separation of the daughter elements is least advanced have a horse-shoe shape. In others, the daughter elements are parallel and widely separated. In a few, the separation is incomplete, the ends only remain apposed, giving the appearance of rings. In fig. 13 this cell has a striking resemblance to a heterotypical mitosis such as occurs in testis. Its cytoplasm is clear and voluminous, and there are no intercellular bridges between it and the surrounding epithelial cells. The number of chromosomes in the cell, however, is not diminished, but amounts to 45 to 50 when both sections are examined. Such a mitosis, instead of reducing the number to half, really results in the original number of chromosomes being doubled, because the separated halves of the chromosomes combine again to form a single nucleus.

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* T. H. Montgomery, 'Proc. Acad. Nat. Sc., Philadelphia,' 1901; 'Biol. Bull.,' vol. 4, 1903.

† W. S. Sutton, 'Biol. Bull.,' vol. 4, 1902.

After elimination of these sources of confusion, there remain other apparent heterotypical mitoses which cannot be explained in any of these ways. The chromosomes present an irregular contour and become drawn out like a viscid fluid in the later stages of separation. Individual chromosomes cannot be made out. The achromatic spindle develops at such a rate that the evolution of the chromosomes cannot keep pace with it, and they are drawn towards the spindle and stretched upon it before they have completely contracted and condensed.

All these abnormalities may occur in nuclei possessing the usual number of chromosomes. They also occur in cells with a greater or lesser number associated with the presence of multipolar and asymmetrical mitoses in other cells. In such cases there is no evidence warranting the assumption that the diminution in the number of the chromosomes is due solely to a nuclear division effecting a reduction comparable to that of the sexual cells.

Galleotti‡ and von Hansemann§ have shown that nuclei with diminished numbers of chromosomes (hypo-chromatic) may arise from larger ones by asymmetrical mitosis, in which entire chromosomes pass to one daughter cell, because they are only attached to one or other attraction sphere, and also by "casting out of chromatin." "Casting out of chromatin" is merely an exaggeration of what occurs in asymmetrical mitosis; in it some chromosomes remain unattached to either attraction-sphere, and therefore fail to be included in either daughter nucleus. Krompecher* and we ourselves† have shown that multipolar mitoses may also lead to a diminution in the number of chromosomes. We stated that nuclei with diminished and half the somatic number of chromosomes occur without it being possible to determine whether the diminution has been effected by asymmetrical mitosis, casting out of chromatin, multipolar or heterotypical mitosis.

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* Th. Boveri, 'Sitz.-ber. Phys.-med. Ges.,' Würzburg, 1897; 'Zellenstudien,' vol. 4, Jena, 1901.

† M. Boveri, 'Jen. Zeitschr. f. Naturwiss,' vol. 37, 1903.

‡ 'Ziegler's Beitr.,' vol. 14, 1893.

§ *Loc. cit.*

We have given our reasons for now believing that the mitoses we formerly assumed confirmed the occurrence of a heterotypical reducing division in cancer, are, in reality, somatic mitoses. Although we do not presume to explain in the above manner all the figures which may be brought forward resembling that form of nuclear division, we submit that the occurrence of heterotypical mitoses in cancer requires further proof. Multipolar mitosis and other irregular forms of cell-division occur in cancer, but they do not supervene upon heterotypical mitosis. They are entirely independent of its presence, and, of themselves, suffice to account for the diminutions frequently occurring in the number of chromosomes in cancer throughout the vertebrates.

DESCRIPTION OF PLATES.

[Plates 5 and 6.]

Fig. 1.—Apparent heterotypical mitosis. Transplanted carcinoma of mouse. Analysis of ring, loop, and bivalent chromosomes (heterotypical). Replica of fig. 3 of Royal Society paper, and of fig. 27, First Scientific Report, 1904. × 3000/1.

Fig. 2.—Same section as fig. 1. Analysis after restaining, showing how a fortuitous association of short somatic (longitudinally split) chromosomes gives the appearance of bivalent elements. × 3000/1.

Fig. 3.—Partial analysis of the remainder of the mitosis, of which part only is shown in figs. 1 and 2. Longitudinally split chromosomes with limbs of unequal length lying at various angles to the spindle axis. × 3000/1.

Fig. 4.—Diagram of a somatic amphiaster, in which longitudinally split V-shaped chromosomes, with limbs of unequal length, are apparently arranged parallel to the spindle axis. Adjacent chromosomes, with their longer limbs on opposite sides of the equator, if regarded as together forming one chromosome, would convert such a mitosis into a heterotype with half the somatic number of chromosomes arranged longitudinally on the spindle, *e.g.*, figs. 3, 5, 6, 7, 8, 9, and 10.

Figs. 5 and 6.—Apparent heterotypical mitosis. Fig. 5, replica of fig. 4, Royal Society paper, and of fig. 26 in First Scientific Report, 1904. Transplanted carcinoma of

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* 'Centralb. f. Path. u. path. Anat.,' vol. 13, 1902.

† *Loc. cit.*

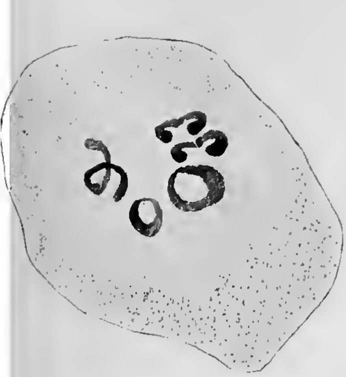


FIG. 1.

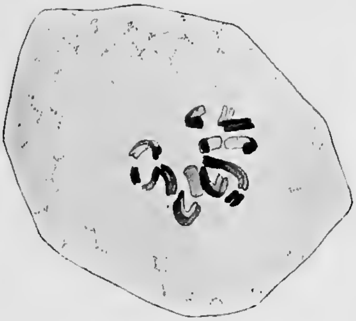
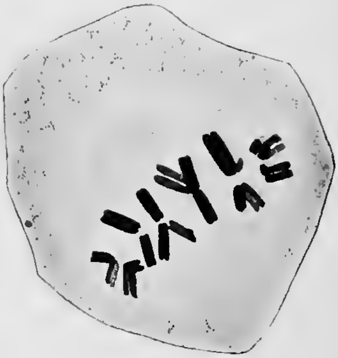


FIG. 2.



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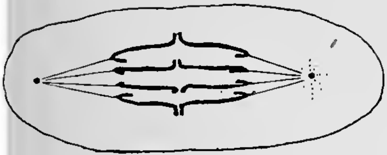

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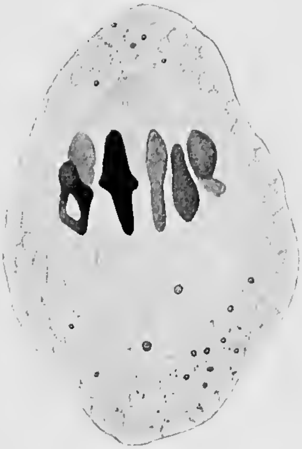
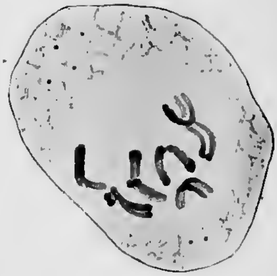


FIG. 6.



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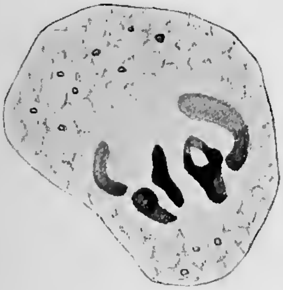
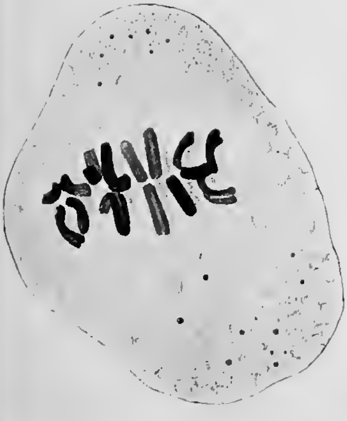


FIG. 5.



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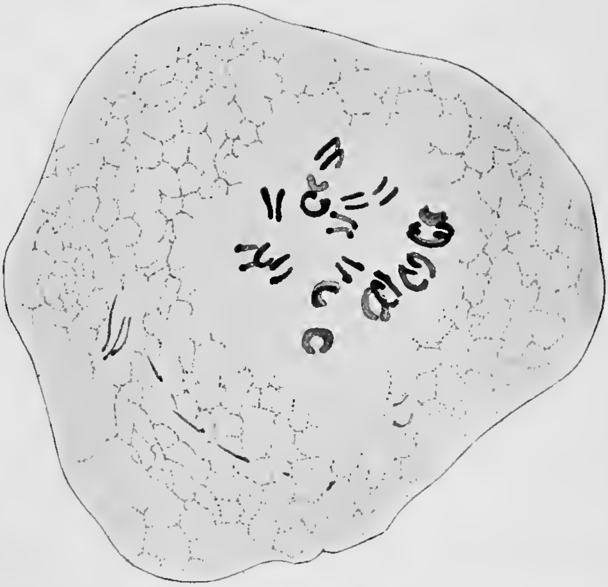

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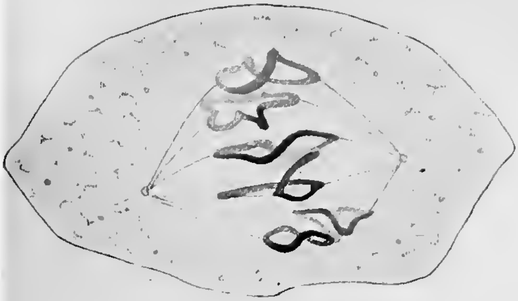

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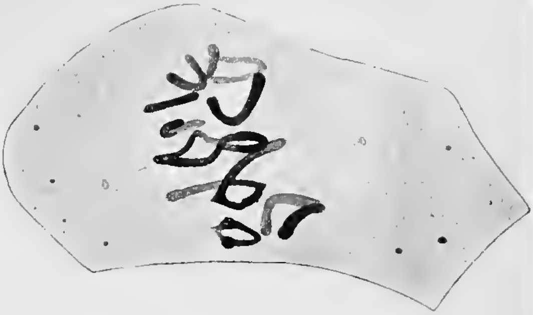

Fig. 10.

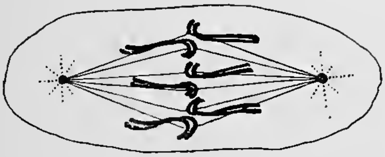

Fig. 11.

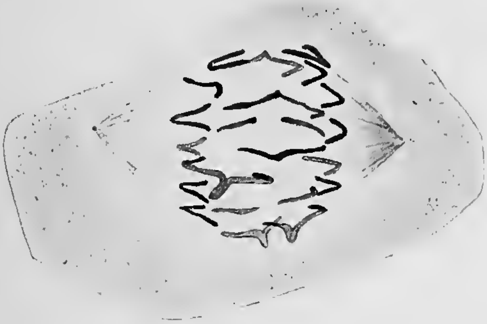

Fig. 12.

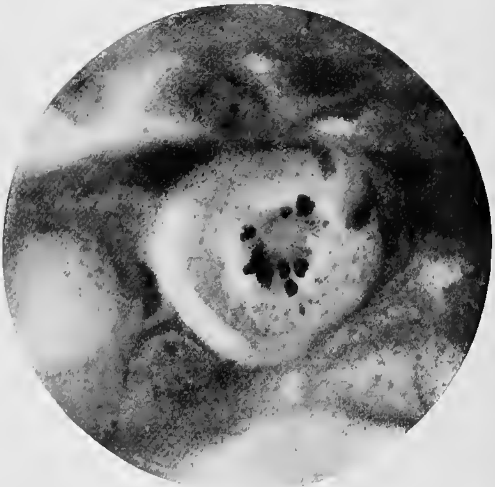

Fig. 13.

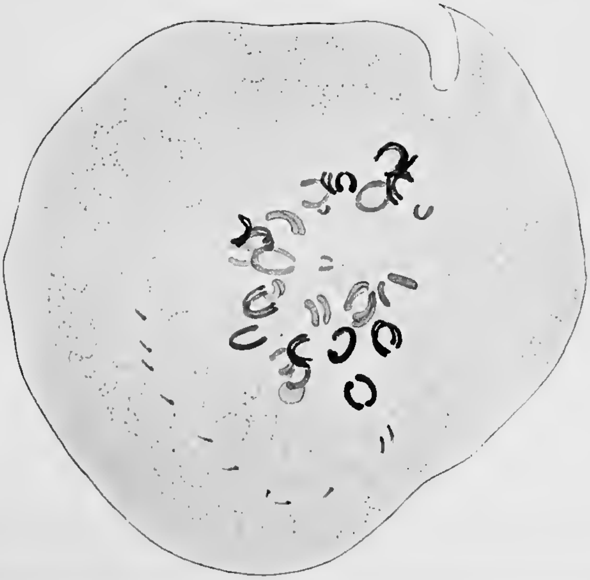

Fig. 14.

mouse. Chromosomes arranged longitudinally on the spindle. The mitosis is contained in two consecutive sections. × 3000/1.

FIGS. 7 and 8.—Same sections as figs. 5 and 6. Result of analysis after restaining. Longitudinally split chromosomes with unequal limbs projecting above and below the equatorial plane. × 3000/1 of diagram, fig. 4.

FIG. 9.—Apparent heterotypical mitosis. Transplanted carcinoma of mouse. Loop and figure-of-8 chromosomes arranged longitudinally on the spindle. × 3000/1.

FIG. 10.—Analysis of the same preparation as fig. 9, showing the slight differences in interpretation sufficient to make this mitosis conform to the somatic type. The loop chromosome in the middle of the equatorial plate consists of two distinct V-shaped chromosomes with unequal limbs projecting above and below the equator. The attraction fibres are attached to the apices, and not to the ends of the long limbs as would be the case in a true heterotype. × 3000/1.

FIG. 11.—Diagram of a somatic metaphase in which the limbs of the chromosomes are of unequal length. The longer limbs still cohere after separation of the apices and shorter limbs. The barrel-shaped figure thus produced resembles a heterotype, especially when the compressed form of the cytoplasm crowds the chromosomes together.

FIG. 12.—Shows the detailed analysis of the mitosis at the upper part of fig. 20, Plate 7, Second Scientific Report, 1905. It illustrates the mode of separation of daughter chromosomes with unequal limbs, as represented diagrammatically in fig. 11. Transplanted carcinoma of mouse. × 3000/1.

FIG. 13.—Microphotograph (untouched) of "monaster" mitosis from squamous-celled carcinoma of the tongue (man). Shows ring and U-shaped chromosomes. × 1000/1.

FIG. 14.—Analysis of same section as fig. 13. Partial separation of the daughter chromosomes accounts for the presence of ring and U-shaped chromosomes. No centrosomes or achromatic figure visible. × 3000/1.

FIG. 15.—Remainder of same cell in next section. Shows large number of chromosomes of ring and U-shape, along with others in which the widely separated daughter-rods are parallel to each other. × 3000/1.

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THE PROBLEMS OF CANCER.

By E. F. BASHFORD, M.D.
General Superintendent Cancer Research Fund.

I.—*The Extent of the Field which has been Investigated in Regard to Cancer and its Relation to the Pessimistic Views Entertained in Regard to the Ultimate Results of the Investigation of Cancer.*

Our knowledge of malignant new growths is all but limited to a recognition of the facts which present themselves for investigation in pathological laboratories, obtaining their material from the *post-mortem* or operating theatres of hospitals in the most civilized portions of the world. The material thus obtained has been extensively investigated, from the purely histological standpoint, to a great extent also in co-relation with clinical observations. It is, perhaps, generally conceded that further advances in these directions will not be easy of attainment, and that by these paths alone the problems of cancer will not be solved.

With the materials occurring in hospitals other lines of inquiry, especially biological, bio-chemical, the conditions of growth of cancerous tissue as distinct from the problem of the genesis of malignant new growths, have been hardly touched upon, except in a purely speculative fashion, and in the latter direction to a degree out of all proportion to the meagreness of the facts accumulated.

Speculation in regard to the nature and genesis of malignant new growths has roamed over the full field of biological science and the actual facts constituting our definite knowledge of cancer have been drawn from what by comparison is a singularly limited field, namely, that accessible to the microscopical and other histological methods of the pathological anatomist, for clinical observations have hardly contributed much to the hypothetical discussions of the nature of cancer.

It would seem to be advisable to endeavour to interchange the disproportions existing between the fields from which the facts and the theories of cancer have been drawn, so that instead of speculations from many fields being founded, as at present, upon the few facts of cancer ascertained from its occurrence among the more educated of mankind, facts from a very extensive biological inquiry, embracing not only all races of men, but, so far as possible, the entire animal kingdom, will be focussed upon the condition which is of so much interest to us at present.

Probably in the disproportions of the fields from which the theories and the facts of cancer have been drawn is to be found the explanation of the standstill to which cancer investigation has come since Virchow's classical work has been followed to its logical results. In this disproportion we have possibly also the cause of the prominence obtained by views, which, had the facts of cancer been founded upon a wider basis, would never have had devoted to their attempted establishment the amount of labour which has been conferred upon them. On the other hand, the apparent hopelessness of endeavouring to elucidate the problems of malignant new growths would not have been magnified to such an extent had this disproportion not existed.

Obviously, it behoves those devoting attention to the problems of cancer to endeavour to adjust the inequality, which has been pointed out, in the hope that when the facts of cancer as a general and comparative biological problem, as distinct from a problem of human pathology only, have been placed upon a basis commensurate with the extent of its ramifications in man and animals, the pessimism now prevailing, not without justification, will, with the attainment of this adjustment, disappear.

In amplification of what is implied by endeavouring to regard cancer not merely as a problem of human pathological anatomy, but as a problem of much greater extent, some matters may be alluded to which, if of a speculative nature, seem to indicate the importance of regarding cancer from the standpoint of a comparative biological problem, even at this early stage.

The following aspects of some problems associated with the study of cancer are referred to in the hope that the attention of those having opportunity of making observations may be directed to them.

II.—*The Theoretical Aspects of a Comparative Biological Study of the Nature of "Cancer."*

Biological investigations will probably ultimately form a very important aspect of any research into the nature of cancer, for the problems of malignant new growths are more likely to be elucidated by a general biological investigation, than by mere attention to the conditions obtaining in man, especially in view of the limitations to which investigations in human beings are subject.

At the outset it is necessary to be certain that the new growths occurring in a long series of domestic animals are absolutely identical in nature and consequences with the benign and malignant new growths of man. In regard to the occurrence of "cancer" among wild animals, we have less positive evidence, owing, possibly, to the difficulty of obtaining information of the kind required.

There can be no doubt that some, if not all, forms of malignant new growths occurring in man and animals are identical in nature. It is a matter of very far-reaching importance that the types of malignant and benign new growths are reproduced in very divergent species of animal with such marked similarity in the minute histological details characteristic of the type of new growth. The features characteristic of a type of new growth in man are reproduced in other mammalia with a degree of similarity not found in any other diseased condition to which man and animals are mutually subject.

The reaction of the tissues of different mammalia, due to the presence of any known identical parasitic organism, is more or less characteristic for each species, and the uninitiated would scarcely fail to pronounce tissue reactions due to the action of the same parasite—tubercle, diphtheria, etc., on different species of animal as entirely distinct conditions. The benign and malignant new growths of man and animals are not distinguished by any such characteristic difference, so that one has no hesitation when shown typical conditions presenting themselves, for example, in the liver of the frog, dog, horse, and man, in at once pronouncing them to be exactly analogous processes.

The exhaustive and comparative study of "cancer" in animals in all its features, clinical, pathological, biological, with particular regard to the distribution throughout the higher and lower animals, will probably lead to results of the greatest importance. Malignant new growths or certain types of them might be found to be limited to certain orders, or characteristic distinguishing features be discovered for the new growths of different orders, for example, mammals, birds, reptiles, etc.

The crucial problems of cancer can all be attacked by a study of the conditions in animals, some can alone be approached in animals, and only with them will it be possible to perform experiments bearing on the etiology, pathology, prevention, and attempted cure. In this connexion it may be mentioned that absolutely incontrovertible evidence for or against many prevalent conceptions of the nature and cause of cancer would be obtained, and the questions of parasites, heredity, diet, injury, influence of tobacco pipes, etc., would be definitely settled.

In statistical inquiries the importance of taking account of the age and sex-distribution of a population in determining the relative incidence of cancer has long been recognized. The possible importance of the study of age-incidence as a feature in a general biological inquiry has not hitherto had attention drawn to it.

In this connexion the ideal to be desired is a series of observations so extensive that the age at which the maximum incidence of cancer occurs for each species, and the liability to attack of the various organs can be ascertained. It might thus be possible to define the comparative incidence throughout the animal kingdom, and to ascertain whether or not the maximum incidence in each species, or perhaps in each organ, had a relation to a definite stage in the life cycle of each species. We are, however, only likely to accomplish the compilation of data for the mammalia represented by our common domestic animals. The attainment of even so much would be of the very greatest value.

The length of the human life cycle has been a great impediment to the solution of many problems which can easily be investigated in short-lived animals, for example, the study of heredity, and particularly with regard to the fulfilment of the requirements of Galton's law.

The length of the life cycle in the different species proved to suffer from cancer varies greatly. Cancer in animals occurs as in man, especially in the aged. Old age in the domestic animals is, however, attained at 14 to 20 years, or less. It is obvious, therefore, that identical manifestations first presenting themselves in any number in mankind after 40 years of age, and in the common domestic animals at 14 to 20 years, must pass through the latent non-manifest stages in a much shorter period in the latter. It may be that this latent period will be found to be in strict proportion to the life duration, and be different and definite for each species just as much so as the gestation period.

The fact that such pronounced variations occur in the periods within which identical processes manifest themselves in man and in different species of animals would indicate the important dependence of the development of malignant new growths on circumstances innate in each species of organism, and on the biological laws peculiar to and controlling the growth of each species of animal.

Domestic animals, with the exception perhaps of pet dogs and cats and horses, are not frequently allowed to attain old age; the vast majority are put to death at an early stage in life. The total number reaching the most favourable age for the development of cancer is small. It has of course been asserted that cancer in domestic animals is the result of contact with man. I am not at present concerned with the possibility of the transmission of cancer from one individual to another, but would only point out that man's responsibility in regard to domestic animals may, for all we know to the contrary, be limited to the provision of opportunities for reaching the cancer age. Among wild animals also, in the absence of artificial assistance for the maintenance of life in the struggle for existence, the same factor may enter, and, together with the difficulty of making observations, contribute to the rarity with which the condition is met with among them.

A comparative study of the age-incidence of cancer among domestic and wild animals of varied species will certainly give comprehensive information on the relation of the incidence of cancer to the rapidity with which maturity is attained. Light may also be thrown on the reasons underlying the higher cancer-rate of later life.

For the same reason, exact observations on the age-incidence in the males and females of differing races of mankind among whom also maturity is arrived at, at varying ages, is desirable. A comparison of the age-incidence of cancer in men as contrasted with that in women who attain maturity more rapidly, might also be of value, for example, in India, where puberty is attained at an early age, and the child-bearing period stated to be over at, or about, the thirtieth year.

In the classification of "tumours" no marked advance has been made since Virchow, and on the basis of experience limited to mankind is not likely to be easy of attainment; but with the assistance of the extensive study of tumours in mammalia and other animals, it is reasonable to suppose that an advance would take place and a comparative natural classification be evolved.

Another specific problem—namely "deciduoma malignum," or "chorion-epithelioma"—seems to require consideration from the comparative biological standpoint, and to be more than a problem, merely of interest to obstetricians. It appears to be of great theoretical importance, and therefore it is much to be desired that those who have the opportunity will search for its possible occurrence, or for analogous processes in other mammalia among those with deciduate and non-deciduate placentae.

In cases where animals die after abortion or abnormal gestation, it would be very desirable if a necropsy could be made, and attention particularly directed to the uterus in order to discover, if possible, in other mammalia, anything analogous to the "deciduoma malignum" of mankind. If in any case an abnormal condition be detected, search should be made for secondary deposits in other organs.

It is only fair to point out that in indicating the extensive nature of the field of inquiry thus marked out, it has not been forgotten that the difficulties in attempting to carry it out will be very great indeed. It will involve the co-operation of workers in many professions, and in many trades and fields of scientific inquiry, and years of patient observation. A difficulty met with in mankind presents itself in animals in augmented form; cancer in animals is only likely to be recognized during life if it be situated on the visible, readily accessible, portions of the body; cancer of the internal organs is only likely to come rarely under observation, viz. at necropsies. Among aborigines it is probable that reliable data regarding cancer will be very difficult to obtain, except in those instances where there has been much contact with the white man.

A comparative study of the facts relating to the incidence of "cancer" in the animal kingdom would certainly enable us to orientate ourselves to an extent not likely to be attained through any other line of investigation. It is undesirable at present to speculate whether or not a common biological law applicable to the whole question, or a series of biological laws would be revealed.

Perhaps what has been stated may suffice to show that the prevailing pessimistic views as to the hopelessness of investigating cancer are unjustified in the face of what still remains to be done in this problem. Owing to the fact that cancer has hitherto been considered a subject which concerned only medical men, we are only at the very beginning of the work before us—surely the most inopportune occasion on which to regard it as hopelessly beyond our powers. For the accomplishment of the work to be done it is too much to require the mere medical man to do all in an investigation which extends far beyond the province of medicine into those of general biology, ethnology, zoology, and embryology. Is it too much to hope that workers in these fields will appreciate the importance of their share in attempts to ascertain the cause and nature of the malignant new growths of man and animals? What is most needed at present is a definition of the distribution of the various types of malignant new growths throughout the animal kingdom.

In conclusion, I should like to add that the ideas forming the basis of the above remarks have taken on a more definite form in consequence of much discussion with Dr. J. A. Murray.

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THE COMPARATIVE STUDY OF CANCER.

BY

E. F. BASHFORD, M.D.,
Imperial Cancer Research Fund.

SECRETARY AND DIRECTOR:
E. WHITE WALLIS, F.S.S.

OFFICES
PARKES MUSEUM, MARGARET STREET,
LONDON, W.

[Excerpt from Vol. XXV., Part III., 1904, of the Journal of The Royal Sanitary Institute.]

THE COMPARATIVE STUDY OF CANCER.

By E. F. BASHFORD, M.D.,

Imperial Cancer Research Fund.

A FEW years ago Professor McFadyean was obliged to protest against the assertion of a distinguished member of the medical profession that cancer was a disease limited to man. Veterinarians have described in the domesticated mammals practically all the forms of malignant new growths recognised in man with the exception of what is known as deciduoma malignum or chorio-epithelioma, associated with pregnancy. It is also very doubtful if an authentic case of cancer of the uterus has been described in an animal.

It now seems probable that a liability to some form of cancer is one of the conditions under which the life of all vertebrates is passed. If allowance is made for variations in the minute and gross anatomy of the vertebrates, cancer presents the same fundamental characters in all the animals in which it occurs. It also exhibits a curious contrast to the infectious diseases common to man and animals, in that, with identity in the nature of the disease and in its manifestations in various species, there is an entire absence of transmissibility from an animal of one species to another individual of a strange species. Further, cancer as cancer produces no symptoms which are peculiar to it, such as characterise the reaction of the tissues, or of the organism as a whole, to various infective agents.

We must therefore look upon the cases of cancer which present themselves sporadically in different vertebrates as having no connection with one another, as having arisen "de novo" in each individual in which they are found. These are some of the considerations which have sprung from studying cancer from the comparative standpoint, which, together with the results of experimental and biological investigations, promises to give a new impetus to the investigation of cancer. The problem as it presents itself at present is how, when, and why malignant new growths arise "de novo" in the course of the life of many vertebrates.

Benign new growths behave as independent parasitic organisms, Everything which characterises a benign new growth as an independent organism is also characteristic in enhanced degree of a malignant new growth. It is not proposed to discuss how and why malignant new growths arise, but only to draw your attention to the time when they come under observation, which of course may be a very different thing from the time at which they have arisen.

One of the fundamental characters of cancer, especially carcinoma, is that it shows a curious predilection for the later adult and old age periods of life in man and in all the various species of animals subject to it. Although this is now a well known fact, I venture to draw the attention of the veterinary profession to it, because associated with it there is a question to which only the veterinary profession, to the members of which the Imperial Cancer Research Fund is already greatly indebted, have the opportunity of giving the answer, by helping to accumulate the necessary facts.

The duration of life varies greatly in the species subject to cancer. Old age is therefore attained quickly or slowly, if the absolute number of years be considered. Cancer is an identical process in all animals, and shows itself at a time which is in direct proportion to the varying durations of life, and is therefore definite and different for each species. These relations of the cancer ages to the durations of the span of life indicate the important dependence of the development of malignant new growths as a whole, upon circumstances innate in each species of organism, and on the laws peculiar to and controlling their growth. At present we can only draw this general conclusion, and speculate as to its cause and its coincidence with the wane in reproductive activity.

We require more information. Even in the case of the most common domesticated mammals we have no data extensive enough to permit of an instructive comparison of the relative frequency with which different animals suffer, nor which allow us to single out the sites of greater susceptibility, or determine whether these are the same or different in various animals, and in the two sexes. Epithelioma is the form of new growth of which the Imperial Cancer Research Fund has received most specimens. Many of these have come from the horse, cattle, dog, cat; also from the hen, and some doubtful cases from the trout.

It appears to me, however, that one is not justified in assuming that epithelioma is relatively more frequent than other forms of cancer. The apparent frequency of epithelioma may be only a consequence of its occurring on surfaces where it is more easily observed than internal cancers which are only likely to be found in numbers when numerous post-mortem examinations are made. This view receives some support from the fact that in the case of those domesticated mammals which are slaughtered for food and the carcases submitted to meat inspection a larger number of internal cancers have been received. The noteworthy omission of the sheep, goat, and pig may not represent an insusceptibility to epithelioma in the case of these animals.

All the cases of epithelioma above referred to have been obtained from relatively old animals. All the tumours received by us from sheep, goat, pig have been from relatively young animals. In the case of the animals slaughtered for food, viz.: cattle, sheep, pigs, etc., for slaughtering they are preferred at the youngest age which yields profit, *e.g.*, 53,482 pigs were slaughtered in Glasgow in 1903. The average age of these was 6—12 months. No case of cancer was found. This does not prove that the pig is relatively exempt from cancer, and I put the question—will no case of cancer be found if the carcases of 50,000 old pigs are examined with the same care? In the case of the cow, considerable numbers may be kept to higher ages for milking and breeding purposes by poorer people, *e.g.*, in Ireland. We can segregate cows into groups of younger and older animals, and where this segregation is possible, *e.g.*, in Glasgow, we find a preponderance of cancer in the latter group.

Is the presence or absence of a considerable proportion of middle-aged and old individuals the only factor which determines the frequency with which cancer occurs in different animals? Or are there really species of domesticated and wild animals among which even with a considerable proportion of aged individuals cancer is not to be found? If such animals exist, the reasons for their natural exemption, or for the natural exemption of any of their organs, from cancer may be of theoretical and practical importance.

Even in man, where cancer has been longest known and is still most frequently recorded, only a proportion of the total number of cases is recognised. This proportion approximates more nearly to the absolute number occurring, in accordance with the thoroughness with which cancer is looked for. Many cases are discovered only in consequence of post-mortem or microscopic examination. Under the conditions of human life it is unreasonable to expect that all cases of cancer will ever be brought to light, we have to be content with an approximation to the total, with the recorded frequency as distinct from the absolute frequency. Theoretically we could arrive at the absolute frequency were it possible to have such an extensive series of autopsies that the subjects could be distributed in the age proportions characteristic of a standard population.

In the case of domesticated animals, more especially those which are slaughtered for food, and therefore subjected to meat inspection, the machinery necessary to detect the absolute frequency of cancer among them already exists, if the meat inspectors and their assistants know how to recognise cancer. So far as I am aware the careful systematic meat inspection conducted under Mr. Trotter's direction has done more to give us a true idea of the relative frequency of cancer in animals slaughtered for food than the work in any other abattoir. Conditions which are impossible of attainment in the case of mankind are practically obligatory in the case of all animals slaughtered in public abattoirs where the carcases are submitted to skilled post-mortem examination. The results obtained in the Moore Street Abattoir, Glasgow, under the able direction of Mr. A. M. Trotter, show that the machinery for meat inspection is sufficient to give most valuable information on the comparative age, sex, and organ incidence of cancer in *e.g.*, cattle, sheep, and pigs.

There is one other point on which skilled meat inspection can yield most valuable information. It is recognised that castration prevents the acquisition of the secondary sexual characters, prolongs the period of growth, and generally delays the tissue changes which distinguish younger from adult and older individuals. The sexual organs have a profound influence on the body, and it was natural that their possible influence on cancer should receive attention. Dr. Beatson, of Glasgow, was the first to perceive that the removal of the ovaries in inoperable cancer of the breast in women sometimes had a beneficial result. During the past year we have examined a number of cancers obtained from geldings, and from castrated or spayed cattle, dogs, and cats. This shows that the simple absence or presence of the *normal* internal secretion of the reproductive organs cannot determine the initiation of the cancer process, nor is the presence of an *abnormal* secretion by the reproductive organs a necessary preliminary condition. These possibilities are excluded by the occurrence of cancer both in the presence and in the absence of these organs themselves. I have already pointed out the curious coincidence between the time of the maximum tendency to cancer and the period of waning reproductive activity. This may or may not be only a coincidence. In the course of meat inspection it is possible to determine whether the age at which cancer tends to occur in spayed or castrated animals is earlier or later than in entire animals, and these data will give the first reliable indication of whether or not the reproductive organs exercise any influence in determining the coincidence of the higher cancer rate with later adult life.

The extent to which careful meat inspection in Glasgow and fish inspection in Nottingham and at Billingsgate have been responsible for the detection of cancer in animals destined for food consumption has been emphasised. There can be no doubt that the inspectors at abattoirs and fish and poultry markets will in future detect cancer and the facts associated with its occurrence more frequently if they will only look for it. The Imperial Cancer Research Fund will most willingly continue to examine and report on the nature of tumours from all animals if the age, sex, and animal are stated, together with information as to whether the animal was castrated or entire. In drawing special attention to the carcases of animals killed for food, I should not omit to state that equal importance attaches to data from the horse, dog, cat, and any other animal whatsoever.

I have tried to point out to you some matters on which the veterinary profession can supply valuable information, and by doing so place the public and those whose duty it is to investigate the nature of cancer under great and lasting obligation. The members of the veterinary profession have the opportunity of obtaining this information, and that the present machinery is adequate to yield valuable results the facts brought to light in the Glasgow abattoirs have fully demonstrated. More extended observations of the same kind may contribute materially to the relief of human suffering.

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